REMARKS

STATUS OF THE CLAIMS

Claims 1-72 were pending. Claims 7, 9, 14-16, 34-42, 71 and 72 have been withdrawn from consideration. Independent claims 1 and 43 have been amended to clarify that alteration of chromatin structure facilitates access to cellular chromatin by other molecules and to correct antecedence in claim 43. Support for the amendments is discussed in detail below. Thus, claims 1-6, 8, 10-13, 17-33 and 43-70 are pending as shown above.

INTERVIEW SUMMARY

Applicants thank Examiners Akhavan and Leffers for conducting a telephone interview on October 27, 2004 with the undersigned and Dr. Sean Brennan of Sangamo BioSciences, Inc. The rejections under 35 U.S.C. § 112, first paragraph (new matter and enablement) were discussed. Although agreement was not reached, potential claim amendments to obviate the new matter rejection were discussed and have been incorporated herein. With regard to enablement, Applicants were encouraged to submit references showing *in vivo* function of fusion proteins comprising a DNA binding domain and a functional domain.

35 U.S.C. § 112, 1ST PARAGRAPH, WRITTEN DESCRIPTION, NEW MATTER

Claims 1-6, 8, 10-13, 17-33 and 43-70 were rejected under 35 U.S.C. § 112, first paragraph. (Office Action, page 3). In particular, it is maintained that the original disclosure fails to specify subject matter regarding "fusion molecule does not regulate transcription" as claimed. *Id.* In support of this new matter rejection, selected portions of the specification are cited in the Office Action.

Applicants traverse the rejection and supporting remarks.

It is well settled that the proscription against the introduction of new matter in a patent application (35 U.S.C. 132 and 251) serves to prevent an applicant from adding information that goes beyond the subject matter originally filed. See, *e.g., In re Rasmussen*, 650 F.2d 1212, 1214, 211 USPQ 323, 326 (CCPA 1981) and MPEP § 2163.06. The Office Action implies that literal support is required, when, in fact, M.P.E.P. § 2163.02 specifically indicates the reverse, namely:

> The subject matter of the claim need not be described literally (*i.e.*, using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement.

Thus, the written description requirement is satisfied if the specification reasonably conveys possession of the invention to one skilled in the art. *See, e.g., In re Lukach,* 169 USPQ

795, 796 (CCPA 1971). The disclosure must be read in light of the knowledge possessed by the skilled artisan at the time of filing, for example as established by reference to patents and publications available to the public prior to the filing date of the application. *See, e.g., In re Lange,* 209 USPQ 288 (CCPA 1981). Moreover, the burden is on the Examiner to provide evidence as to why a skilled artisan would not have recognized that the applicant was in possession of claimed invention at the time of filing. *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111 (Fed. Cir. 1991); *In re Wertheim,* 191 USPQ 90 (CCPA 1976).

In the pending case, the as-filed specification clearly conveys that Applicants were in possession of methods involving fusion proteins that do not in and of themselves regulate transcription.

Nonetheless, to expedite prosecution, Applicants have replaced this phrasing with a positive recitation that remodeling by the fusion protein facilitates access to cellular chromatin by a second molecule. Applicants note that the amendments do not raise any issues of new matter, as they simply clarify the nature of how chromatin structure is altered by the chromatin remodeling portions of the claimed fusion proteins.

Indeed, throughout the specification, Applicants indicate that the chromatin remodeling proteins used do not necessarily regulate transcription themselves, but that they facilitate access to cellular chromatin, which may in turn facilitate transcriptional regulation (see, page 4, line 28 to page 5, line 6; page 5, lines 9-16; page 6, lines 14-15; page 12, lines 5-10; page 12, lines 18-19; page 13, lines 6-9, emphasis added):

> Despite this knowledge of the effects of chromatin remodeling on gene expression *in vitro* and *in vivo*, methods for directed manipulation of chromatin structure are not available. Accordingly, for situations in which a regulatory molecule is prevented, by chromatin structure, from interacting with its target site, methods for targeted modification of chromatin structure are needed. Such methods would be useful, for example, to facilitate binding of regulatory molecules to cellular chromatin and/or to **facilitate access** of DNA-binding molecules to cellular DNA sequences. This, in turn, would facilitate regulation of gene expression, either positively or negatively, by endogenous and exogenous molecules, and provide additional methods for binding these molecules to binding sites within regions of interest in cellular chromatin.
>
> Disclosed herein are compositions and methods useful for targeted modification of chromatin. These compositions and methods are useful for **facilitating processes that depend upon access of cellular DNA sequences to DNA-binding molecules**, for example, transcription, replication, recombination, repair and integration. In one embodiment, targeted modification of chromatin facilitates regulation of gene expression by endogenous or exogenous molecules,

by providing access to cellular DNA sequences. Modification is any change in chromatin structure, compared to the normal state of the chromatin in the cell in which it resides.

Modification of chromatin structure will **facilitate many processes that require access to cellular DNA**.

Disclosed herein are compositions and methods useful for modifying chromatin structure in a predetermined region of interest in cellular chromatin. Modification of chromatin structure **facilitates many processes involving nucleotide sequence-specific interaction of molecules with cellular chromatin**. In certain embodiments, modification of chromatin structure is a prerequisite for binding of a regulatory molecule to its target site in cellular chromatin. Such binding can be useful in the regulation of an endogenous cellular gene by one or more endogenous and/or exogenous molecules.

Alterations in chromatin structure in the vicinity of the promoter, mediated by the recruited remodeling complex, **facilitate subsequent interactions** that result in transcriptional activation or repression.

Chromatin remodeling ensues in the vicinity of the target site, which renders the region of binding (*e.g.*, a gene promoter) susceptible to the action of endogenous regulatory factors, and/or to the regulatory activities of exogenous molecules.

Therefore, a skilled artisan would have plainly recognized that that Applicants were in possession of fusion proteins as claimed, namely fusion proteins that facilitate access to cellular DNA by remodeling chromatin structure. Moreover, Applicants maintain that these passages from the specification, *inter alia*, clearly communicate to one of skill in the art that Applicants were in possession, at least as early as the filing date of the present application, of fusion proteins that alter chromatin structure but do not regulate transcription.

In view of these facts and the failure of the Office to provide evidence as to why the skilled artisan would not have understood that Applicants were in possession of the subject matter of the pending claims, withdrawal of this rejection is respectfully requested.

35 U.S.C. § 112, 1ST PARAGRAPH, ENABLEMENT

Claims 1-6, 8, 10-13, 17-33 and 43-70 were rejected under 35 U.S.C. § 112, first paragraph as allegedly not enabled by the specification as filed. (Office Action, pages 4-8). It was acknowledged that the specification enables *in vitro* methods but was alleged that it does not enable *in vivo* methods. *Id.*

As discussed during the telephone interview, the specification teaches various in vivo applications of the claimed methods, for example on page 51, lines 18-22:

> Targeted modification of chromatin structure, as disclosed herein, can be used in processes such as, for example, therapeutic regulation of disease-related genes, engineering of cells for manufacture of protein pharmaceuticals, pharmaceutical discovery (including target discovery, target validation and engineering of cells for high throughput screening methods) and plant agriculture.

Thus, the specification as filed enables *in vivo* uses of the claimed methods.

Further evidence of enablement is attached hereto as Appendices A to C. In particular, these articles establish that the functional domain of a fusion protein (comprising a DNA binding domain and the functional domain) performs the same function *in vivo* as it does *in vitro*. Rebar *et al.* (Appendix A) disclose that a fusion of a zinc finger DNA binding domain and a transcriptional activation domain induces transcription of the VEGF gene, which results in angiogenesis in an *in vivo* mouse model. Similarly, Dai et al. (Appendix B) disclose *in vivo* induction of VEGF expression and resultant angiogenesis in an *in vivo* rabbit model. Van Eenennaam et al. (Appendix C) demonstrate that fusion proteins comprising a zinc finger DNA binding protein and a maize transcriptional activation domain act *in vivo* (in whole plants) to increase transcription of the GMT gene.

These references establish that DNA binding domains fused to a functional domain target the functional domain to a particular region of cellular chromatin and, moreover, that the functional domain is active *in vivo*. Given that fusions of DNA binding domains and transcriptional activation domains work both *in vitro* and *in vivo* to modulate transcription, a skilled artisan would expect that fusions of DNA binding domains and chromatin remodeling proteins would also work both *in vitro* and *in vivo* to remodel chromatin, as set forth in the pending application.

In sum, Applicants have provided ample factual evidence demonstrating that the specification enables the pending claims throughout their scope and withdrawal of the rejection is respectfully requested.

OBVIOUSNESS-TYPE DOUBLE PATENTING

Claims 1-6, 8, 10-13, 17-33 and 43-70 were provisionally rejected under the judicially created doctrine of obviousness type double patenting over claims 1-33 and 44-71 of co-pending Application No. 10/084,826.

Since the pending application is the parent of USSN 10/084,826, Applicants request that the double patenting rejection be addressed in USSN 10/084,826.

CONCLUSION

Applicants respectfully submit that the claims are in condition for allowance. If the Examiner notes any further matters which the Examiner believes may be expedited by another telephone interview, the Examiner is requested to contact the undersigned.

Respectfully submitted,

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